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Contribution of Cytochrome P450s to Development of Insecticide Resistance in *Musca domestica L.*: A Review

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REVIEW
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ABSTRACT

Musca domestica L. (Diptera: Muscidae) is recognized as one of the most prevalent fly species globally, playing a significant role in the transmission of infections and pathogens that are important in both veterinary and medical contexts. This includes the dissemination of eggs from intestinal helminths, as well as ectoparasites, endoparasites, and protozoan cysts. Several approaches to combating insect pests include biological, physical, chemical, and agrotechnical methods. Chemical methods remain the main strategy for controlling the population of insect pests; however, excessive use, increased dosages, and frequency of treatments have led to the development of resistance. To date, numerous documented cases of resistance to insecticides have been registered in natural populations. A significant mechanism for resistance development is the detoxification of xenobiotics by enzymes of the cytochrome system. This study aimed to summarize the current knowledge on the role of *P450* monooxygenase in developing insecticide resistance in houseflies. This overview focuses on the diversity of Cytochrome *P450* monooxygenases in *Musca domestica* that contribute to resistance against the most popular classes of insecticides and their location in the genome. Throughout this work, the main *P450* candidate genes associated with insecticide resistance were identified and described. The authors also summarized and systematized recent research results in this area.

Keywords: Gene expression, Housefly, Insecticide, Insecticidal resistance, Monooxygenase, Cytochromes *P450*

INTRODUCTION

Currently, *Musca domestica* is one of the most common fly species around the world. Living in perpetual close contact with humans and animals. It is a vector for more than 100 species of bacterial, viral, and fungal pathogens. It also carries worm eggs, cysts, and trophozoites of protozoa (Adenusi et al., 2013; Al-Aredhi, 2015; Nayduch and Burrus, 2017; Issa, 2019; Geden et al., 2021). This species is most commonly found in restaurants, hospitals, landfills, and agricultural facilities (El-Sherbini and El-Sherbini, 2011). Chemical insecticides remain the first line of defense in insect pest control (Freeman et al., 2019). However, extensive use of different insecticides has led to the development of resistance. To date, *Musca domestica* has identified more than 460 cases of resistance to various classes of insecticides. There are four main mechanisms for the development of insecticidal resistance including changes in the permeability of the integument, target site resistance, metabolic resistance, and behavioral resistance. Changes in the permeability of the integument occur due to thickening or changes in the composition of the cuticle of insects. Consequently, these changes prevent insecticide molecules from entering the insect's body (Balabanidou et al., 2018). Target site resistance primarily arises from modifications (mutations or losses) in the protein-coding region of the target site of the insecticide, which leads to incompatibility of the target site for activation. Mutations in the same target gene often cause resistance to the same insecticide in different insect species. The four main types of resistance to various drugs include modified acetylcholine esterase-based (MACE), knockdown resistance (KDR), nicotinic acetylcholine receptor-based (nAChRs), and duplication of resistance to dieldrin (RDL, Khan et al., 2020). Metabolic resistance develops due to enhanced detoxification, which usually stems from overexpression of *CYP450* monooxygenases, nonspecific esterases, glutathione S-transferases, and uridine diphosphate (UDP)-glycosyltransferases (Li et al., 2012; Lopatina and Eremina, 2018; Khan et al., 2020; Pu and Chung, 2024). Behavioral resistance refers to an aversion to insecticides caused by simple repulsion and avoidance, or by an acquired factor (Zalucki and Furlong, 2017). Therefore, the current study aimed to summarize the current knowledge on the role of *P450* monooxygenase in developing insecticide resistance in the housefly.

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Data collection

The data was obtained by searching publications in databases such as Google Scholar, PubMed, Web of Science, and Scopus by keywords including housefly, insecticides, monooxygenase, resistance, cytochromes *P450*, and gene expression. The criteria for selecting publications included, the study subject being *Musca Domestica* L.; Changes in the expression of *P450* monooxygenase genes; and the presence of insecticidal stress. Publications before 2000 were not included in the study. Moreover, experimental articles were mainly considered. Thus, the search for the keywords "*Musca domestica"* and "Housefly" yielded a total of 5131 publications. When adding other keywords, the final number of publications was reduced to 272. These articles were analyzed, and only those publications in which the level of *P450* gene expression changed under the influence of insecticides were selected, resulting in no more than 52 suitable publications.

General characteristics of cytochromes *p450*

The metabolism of xenobiotics, including pesticides, depends heavily on cytochromes *P450* (Scott, 2001). Cytochromes are typically localized in the smooth and rough endoplasmic reticulum or the mitochondria (Cribb et al., 2005; Rewitz et al., 2006). Most *P450* enzymes associated with xenobiotic metabolism are membrane-bound and are located in the endoplasmic reticulum. They possess an N-terminal zone which includes a transmembrane helix responsible for lodging (Feyereisen, 2012). Cytochrome *P450*-dependent monooxygenases play a significant role in the metabolic system, regulating the titers of endogenous compounds, such as hormones, fatty acids, and steroids, as well as in the catabolism and anabolism of xenobiotics, such as pharmaceutical products, pesticides, and plant toxins (Parolini, 2020). These enzymes are found in the organs and tissues of a diverse range of organisms including mammals, fish, plants, arthropods, fungi, and bacteria (Feyereisen, 2005). Monooxygenases in insects were first detected in 1965 (Brooks, 2008). There are 146 *CYP* genes in the genome of the housefly (Scott et al., 2014), and a significant amount of them have not yet been functionally defined.

Insecticidal resistance to pyrethroids

Pyrethroids are classified as neurotoxins; they disrupt the metabolism of sodium and calcium ions, and depolarize the membrane, which leaves the insect paralyzed (Chrustek et al., 2018). Pyrethroids are the most commonly used insecticides against houseflies, and the development of resistance to pyrethroids presents a significant challenge today (Scott, 2016; Khan et al., 2017; Wang et al., 2019). For example, the metabolic resistance of the housefly to insecticides has been most thoroughly described for the Learn Pyretroid Resistant (LPR) strain, which is resistant to unsubstituted phenoxybenzyl pyrethroids. This strain was established through laboratory sampling of houseflies captured in 1980 from a dairy factory in New York City, following four years of localized indoor spraying with permethrin (Kasai and Scott, 2000). Biochemical studies on this strain revealed the *P450* isoform, responsible for pyrethroid detoxification as *CYP6D1*. Overexpression of this gene is correlated with resistance to pyrethroids. It has been demonstrated that, at the time of xenobiotic detoxification, *CYP6D1* expression is ninefold higher in LPR specimens than in sensitive strain specimens (Karunker et al., 2008). Overexpression of CYP6D1 is due to increased gene transcription (Kasai and Scott, 2000; Markussen and Kristensen, 2010). *CYP6D1* is also one of the most well-studied *P450* genes involved in the development of insecticide resistance in houseflies (Freeman, 2020; You et al., 2022). A study on the deltamethrin-resistant (BJD) and the sensitive (TJS) strains revealed that enhanced expression of the *CYP6A40*, *CYP6D8*, and *CYP6G4* genes is associated with pyrethroid resistance. Altogether, *CYP6G*4 is not transcribed in eggs and larvae, and *CYP6A40* and *CYP6D8* are expressed at all life stages of the houseflies (Gao et al., 2012).

Insecticidal resistance to neonicotinoids

For centuries, humans have utilized the insecticidal properties of nicotine to control insect populations (Steppuhn et al., 2004). Nowadays, nicotine derivatives, such as neonicotinoids, are widely used. They affect postsynaptic nicotinic acetylcholine receptors, which block the transmission of nerve impulses, and the insect dies from overexcitation (Markussen and Kristensen, 2010). Resistance to insecticides from the neonicotinoid class (imidacloprid and thiamethoxam) has been detected in natural populations of *Musca domestica*. Strain 766b, collected in Denmark in 2005, showed 130-fold and 140-fold resistance to imidacloprid, as well as 17-fold and 28-fold resistance to thiamethoxam in males and females, respectively (Markussen and Kristensen, 2010). The 791a strain was obtained from a natural population that was collected in 1997 from a farm located in Store Karleby, Denmark. This strain was highly resistant to pyrethroids, dimethoate, propetamphos, methomyl, and azamethiphos, and had some resistance to cyromazine and fipronil (Kristensen et al., 2001; Kristensen and Jespersen, 2003; Kristensen et al., 2004). Selection with imidacloprid 791a increased resistance to imidacloprid by 75-fold in males and 150-fold in females, whereas selection with

thiamethoxam showed minimal effect. Three cytochrome *P450* genes—*CYP6A1*, *CYP6D1*, and *CYP6D3*—were overexpressed in resistant strains compared to the laboratory-sensitive strain (Markussen and Kristensen, 2010).

Insecticidal resistance to spinosad

Spinosad is an insecticide whose active toxins (spinosin A and D) are produced by the soil actinomycete *Saccaropolyspora Spinoza* (Hertlein et al., 2011). The mechanism of action of spinosad is unique; it first targets the nicotinic acetylcholine receptor and subsequently affects GABA receptors (Elsayed et al., 2022). A comparison of *P450* gene expression levels among three *Musca domestica* strains allowed for the identification of genes associated with spinosad resistance (Højland et al., 2014; Højland and Kristensen, 2017). Two resistant strains were analyzed including strain 766b, resistant to imidacloprid and thiamethoxam, and strain 791spin, derived from multidrug-resistant strain 791a through selection with spinosad. It should be noted that the selection with spinosad not only led to the development of resistance to this insecticide but also caused a reduced resistance to fipronil, imidacloprid, and thiamethaxam, which was characteristic of the parental strain 791a. The sensitive WHO-SRS strain obtained in 1988 at the University of Pavia, Italy, was used for comparison as a reference strain. The findings of the study revealed that 19 out of 100 *P450* genes associated with insecticide resistance, including *CYP4D9*, *CYP4D63*, *CYP4D2*, *CYP4G13*, *CYP4G98*, *CYP6A1*, *CYP6A24*, *CYP6A36*, *CYP6A37*, *CYP6D1*, *CYP6D3*, *CYP6G4*, *CYP6G7*, *CYP6G1*, *CYP9F12*, *CYP12A1*, *CYP12A2*, *CYP12G2* and *CYP313D1*. The highest expression among the *P450* genes was characteristic of the *CYP4D63* and *CYP6A24* genes in both resistant strains. Additionally, the *CYP4G98* and *CYP6G7* genes were overexpressed in strain 766b compared to WHO-SRS and 791spin, which indicates their significant contribution to resistance to neonicotinoids. Furthermore, *CYP4D9* demonstrated increased expression in the 791spin strain compared to spinosage-sensitive strains, indicating its important role in the formation of spinosage resistance (Højland et al., 2014; Højland and Kristensen, 2017; Mahmood et al., 2016).

Insecticidal resistance to various classes of insecticides

The Alabama house fly strain (ALHF), which is resistant to several insecticides (permethrin, deltamethrin, fipronil, imidacloprid, chlorpyrifos, etc.), was collected in 1998 from a poultry farm in Alabama (Liu and Yue, 2000). In this strain, 86 of the currently known 146 *P450* genes were expressed. Researchers from Auburn University, Alabama, performed a comparative analysis of *P450* gene expression in a resistant strain of ALHF and sensitive strains, abyss and CS. As a result, they identified 11 genes with expression levels more than 2-fold higher in the multidrug-resistant line compared to the sensitive strains. The identified genes were primarily related to *CYP4* and *CYP6* (*CYP4G13*, *CYP4G99*, *CYP4S24*, *CYP4E10*, *CYP4E11*, *CYP6A36*, *CYP6A40*, *CYP6A52*, *CYP6A58*, *CYP6D3*, and *CYP6D10*; Li et al., 2023). In studies by Zhu et al. in 2008, conducted on the same strain, three additional gene expressions—*CYP4D4*, *CYP4G2*, and *CYP6A38*—were found to be upregulated in response to permethrin exposure (Zhu et al., 2008).

Expression systems are often used to assess the involvement of a gene in the detoxification of specific insecticides, or recombinant proteins are introduced into other insect species. For instance, in several studies conducted in 2022 and 2023, Chinese scientists demonstrated that the *CYP6G4* gene from the multidrug-resistant line of *Musca domestica* can metabolize insecticides of the carbamate class (Zhu et al., 2022, 2023; You et al., 2023). Experiments were conducted in the *E.coli* expression system and *in vivo* on *Drosophila melanogaste*r. The results of the studies demonstrated that *CYP6G4* is capable of metabolizing propoxur through O-depropylation, N-demethylation, and hydroxylation (Zhu et al., 2022). Earlier studies noted that *CYP6A1* and *CYP12A1* are highly expressed in the dianin-resistant Rutgers strain, indicating their ability to participate in the metabolism of organophosphorus insecticides (Li et al., 2007; Højland et al., 2013).

Table 1 depicts the genes responsible for resistance to a particular class of insecticides. To understand the mechanisms underlying the development of insecticide resistance and to design effective methods for its elimination and prevention, it is essential to learn not only which *P450* genes are responsible for resistance development but also their location and regulatory mechanisms.

Table 2 provides information about several *P450* genes and their locations on autosomes (Meisel and Scott, 2018; Li et al., 2023). For some of the genes listed in the table, the location of trans elements that affect gene expression has been studied. Specifically, trans elements located on autosome 1 regulate the *CYP4G99* gene, while those on autosome 2 regulate *CYP4E11*, *CYP6A1*, *CYP6A40*, and *CYP6D3*. The *CYP4G13*, *CYP4S24*, *CYP4E10*, *CYP6A3*, *CYP6A58*, *CYP6D1* genes are regulated by aggregated trans elements located on autosomes 1 and 2. Co-regulation is also typical for elements located on autosomes 2 and 5, which regulate the *CYP6D10* gene (Gao and Scott, 2006; Pu et al., 2016; Li et al., 2023; Freeman and Scott, 2024).

Table 1. *CYP450* enzymes involved in insecticide detoxification in *Musca domestica*

Insecticide class	*CYP* family	*CYP* genes	References
Multidrug resistance (based on the study of the ALHF strain)	*CYP4*	*CYP4G2*, *CYP4G13*, *CYP4G99*, *CYP4D4*, *CYP4S24*, *CYP4E10*, *CYP4E11*	Zhu et al. 2008; Li et al., 2023
	CYP6	*CYP6A5*, *CYP6A36*, CYP6A38, *CYP6A40*, *CYP6A52*, *CYP6A58*, *CYP6D3*, *CYP6D10*	
Pyrethroids	*CYP6*	*CYP6A40*, *CYP6D1*, *CYP6D8*, *CYP6G4*	Karunker et al., 2008; Gao et al., 2012
Neonicotinoids	*CYP4*	*CYP4D9*, *CYP4D63*, *CYP4D2*, *CYP4G98*	Højland et al., 2014, Højland and Kristensen, 2017
	CYP6	*CYP6A1*, *CYP6A24*, *CYP6D1*, *CYP6D3*, *CYP6G4*, *CYP6G7*, *CYP6G1*	Markussen and Kristensen, 2010; Højland et al., 2014; Højland and Kristensen, 2017
	CYP9	*CYP9F12*	Højland et al., 2014; Højland and Kristensen, 2017
	CYP12	*CYP12A1*, *CYP12A2*, *CYP12G2*	
	CYP313	*CYP313D1*	
Spinosyns	*CYP4*	*CYP4D9*, *CYP4D63*	
	CYP6	*CYP6A1*, *CYP6A24*, *CYP6A36*, *CYP6A37*, *CYP6D1*, *CYP6D3*, *CYP6G4*, *CYP6G1*	
	CYP9	*CYP9F12*	
	CYP12	*CYP12A1*, *CYP12A2*, *CYP12G2*	
	CYP313	*CYP313D1*	
Carbamates	*CYP6*	*CYP6G4*	Zhu et al., 2022
Organophosphorus compounds	*CYP6*	*CYP6A1*	Li et al., 2007
	CYP12	*CYP12A1*	Højland et al., 2013

Table 2. Location of some cytochrome *P450* genes in the genome

Autosome	*P450* genes	References
1	*CYP6D1*, *CYP6D3*, *CYP6D10*	Meisel and Scott, 2018; Li et al., 2023
2	*CYP6D8*, *CYP9F12*, *CYP12A1*, *CYP12A2*, *CYP313D1*	Meisel and Scott, 2018
3	*CYP4D9*, *CYP4G13*, *CYP4G2*, *CYP4G98*, *CYP4G99*, *CYP4S24*	Meisel and Scott, 2018; Li et al., 2023
4	*CYP12G2*	Meisel and Scott, 2018
5	*CYP4E10*, *CYP4E11*, *CYP6A1*, *CYP6A36*, *CYP6A40*, *CYP6A52*, *CYP6A58*, *CYP6G4*	Meisel and Scott, 2018; Li et al., 2023

CONCLUSION

At present, the role of some cytochrome P450 genes of *Musca domestica* in the detoxification of several insecticides is well described, particularly the *CYP6D*1 gene. While an increase in expression levels has been noted in response to insecticidal exposure for many *CYP* genes, the specific mechanisms of insecticide detoxification for these genes are still being elucidated. Based on the literature reviewed, it can be concluded that *CYPs* are collectively capable of metabolizing numerous insecticides, but for most insects, there are gaps in terms of which *CYPs* are responsible for the metabolism of a particular insecticide. Additionally, the locations in the genome, linkage groups, and mechanisms of transcription regulation for many *P450* genes remain unknown. More recent publications are interested in this area and more studies are emerging aimed at unraveling the workings of regulatory networks in the context of the development of insecticide resistance. For the most part, the resistance due to the gene activity of the cytochrome monooxygenase family

is polygenic in nature, indicating that resistance to one class of insecticide can be conditioned by several genes. Furthermore, the same genes may be active in conferring resistance to various classes of insecticides, which may contribute to the development of cross-resistance. Thus, molecular genetic studies are essential for each case of insecticide resistance to identify patterns and learn how to predict the development of resistance to other active ingredients. The accumulation of knowledge regarding the insect genome and the mechanisms of resistance to insecticides would facilitate the development of rational strategies for the long-term use of insecticides in pest control programs.

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Availability of data and materials

The data of the current study are available by reasonable requests.

Authors' contributions

Ksenia Krestonoshina conducted project administration, conceptualization, information search and analysis, writing development, and revising. Anastasia Melnichuk did strategic contemplation, information search and analysis, review writing, and editing. All authors reviewed and confirmed the final draft of the manuscript.

Competing interests

The authors have declared no conflicts of interest.

Ethical considerations

All authors have verified all ethical issues including plagiarism, consent to publish, misconduct, data fabrication and/or falsification, double publication and/or submission, and redundancy have been addressed.

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